UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 8, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

15/OPP #
PM52

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

012877

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: September 22, 1998

SUBJECT: OXYDEMETON-METHYL: HED Toxicology Chapter for the Reregistration Eligibility Decision (RED) Document. Chemical No. 058702. Case No. 0258. Barcode D235190.

FROM: Robert F. Fricke
Reregistration Branch 2
Health Effects Division (7509C)
Robert F. Fricke 22Sept 98

THROUGH: Alan P. Nielsen, Branch Senior Scientist
Reregistration Branch 2
Health Effects Division (7509C)
Al Nielsen 9/22/98

TO: Paula A. Deschamp, Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

Attached is HED's toxicology chapter for the Oxydemeton-methyl Reregistration Eligibility Decision (RED) Document.

CC: Cathy Monk/Kathleen Meier
Reregistration Branch II
Special Review and Reregistration Division (7508W)

III. Science Assessment: Oxydemeton-Methyl

B. Human Risk Assessment

1. Hazard Assessment

Oxydemeton-methyl (ODM) is an organophosphorus insecticide, and like all members of this class, the mode of toxic action is the inhibition of cholinesterase (ChE). In all of the studies evaluated in this hazard assessment, the LOEL and NOEL were established by the inhibition of ChE. For the chronic toxicity studies in the rat and dog, the developmental studies in the rat and rabbit, the reproductive toxicity studies in the rat, and the acute and subchronic neurotoxicity studies in the rat, inhibition of brain ChE activity was observed at the LOEL in all of the studies.

In addition to ChE inhibition, the results of a reproductive toxicity studies in the rat showed decreased male and female fertility of non-defined origin. In these studies absolute ovarian and testicular weights were decreased; males also had a high incidence of epididymal vacuolation at histopathological examination. These findings, coupled with positive results found in some of the mutagenicity tests, resulted in several non-guideline studies designed to evaluate and elucidate the potential adverse effects of ODM on reproduction, particularly in the male. In these studies, the reversibility of epididymal vacuolation in rats, the effects of treated males and untreated females on reproduction, and the determination of sperm counts, morphology and motility were evaluated. When results of a reproduction study showed that fertility parameters were unaffected by treatment, even in the presence of 100% epididymal vacuolation, it was concluded that epididymal vacuolation probably has no effect on fertility. These studies also showed, however, that the doses of ODM which cause the reproductive effects, were greater than those doses which produced ChE inhibition.

Even though ODM was found to produce reproductive toxicity, it was not a developmental toxicant. In developmental toxicity studies, in both the rat and rabbit, ODM did not produce any developmental toxicity at doses which produced maternal toxicity. Based on the negative results of these studies and the lack of neurotoxicity (other than cholinergic signs and ChE inhibition), the need for a developmental neurotoxicity study was not required.

In a metabolism study in the rat, urinary excretion was found to be the major route of elimination. In all, two major and five minor urinary metabolites were identified. Two of the minor metabolites, desmethyl ODM and desmethyl ODM sulfone, were of toxicological concern on the basis that they were potentially biologically active. To resolve this question, the desmethylated metabolites were evaluated for their ability to inhibit brain ChE *in vitro*. In this study, brain ChE was not inhibited by either desmethyl ODM or desmethyl ODM sulfone over a wide concentration range; both ODM and chlorpyrifos oxon (positive control) produced inhibition at very low concentrations.

The toxicological data base for ODM is adequate to support reregistration. Even though no guideline subchronic feeding toxicity studies were available for review, a 7-day dermal toxicity

study in rats, several non-guideline 14-day subacute studies in the rat, a subchronic neurotoxicity study in the rat and a 120-day human plasma and erythrocyte ChE study were found to be acceptable. Additionally, acceptable chronic toxicity studies in the rat and dog were available.

a. Acute Toxicity: Acute toxicity studies provide information on the potential for health hazards that may arise as a result of short-term exposure. These data provide a basis for precautionary labeling, protective clothing requirements, and for calculation of agricultural reentry intervals. Sufficient data are available on the acute toxicity of ODM. Acute toxicity values and categories for ODM, technical, and manufacturing product, Mesasystox-R™ [50% a.i. in methyl isobutyl ketone (MIBK), as a stabilizer], are summarized in the tables below. The acute toxicity data requirements 81-1 through 81-6 are satisfied. The acute neurotoxicity studies in the hen (81-7) and rat (81-8) were also satisfied and are discussed in sections h.1) and h.3), respectively.

ODM technical is highly toxic (Toxicity Category I) via the oral and dermal routes exposure. In a primary eye irritation study in rabbits the technical was found to be slightly irritating (Toxicity Category III).

Acute Toxicity of ODM, Technical and Manufacturing Product, Metasystox-R™

Study Type	Animal	Results	Tox Cat	MRID No
ODM, Technical				
81-1: Acute Oral	Rat	Female: LD_{50} = 48 mg/kg	I	40779801
81-2: Acute Dermal	Rat	Female: LD_{50} = 112 mg/kg	I	00143350
81-4: Primary Eye Irritation	Rabbit	Slightly irritating	III	00151801
81-5: Primary Dermal Irritation	Rabbit	Non-irritating	IV	00151801
81-6: Dermal Sensitization	Guinea Pig	Not a skin sensitizer (Beuhler)	N/A	40779802
Metasystox-R (50% a.i. in methyl isobutyl ketone)				
81-1: Acute Oral	Rat	Female: LD_{50} = 96 mg/kg	II	40779803C 40779803
81-2: Acute dermal	Rabbit	Male: LD_{50} = 844 mg/kg	II	40779804C 40779804
81-3: Acute Inhalation	Rat	Female: LC_{50} = 0.427 mg/L	II	40779805C 40779805
81-4: Primary Eye Irritation	Rabbit	Irritant (Probably caused by inerts)	I	40779806C 40779806
81-5: Primary Dermal Irritation	Rabbit	Very slightly irritating	IV	40779807C 40779807
81-6: Dermal Sensitization	Guinea Pig	Not a skin sensitizer (Beuhler)	N/A	40779802

b. Subchronic Toxicity Studies: Subchronic testing requirements for ODM have been met

with acceptable chronic data. In addition, 14-day oral (gavage), feeding, and dermal studies in the rat; a 120-day oral study in human volunteers (see section j.5); a 90-day subchronic delayed neurotoxicity study in the hen (see section h.2); and a 90-day neurotoxicity screening battery in the rat (see section h.4).

c. Chronic Toxicity/Oncogenicity

Sufficient data are available to assess the chronic toxicity and carcinogenic potential of ODM. ODM has been classified as "not likely" to be a human carcinogen; ODM did not alter the spontaneous tumor profile in acceptable carcinogenicity studies in the rat and mouse.

1) Combined Chronic Feeding/Oncogenicity Study in the Rat: In a combined chronic feeding/oncogenicity study [MRID Nos. 00151806, 40865203, 40865201, 40865202 and 44141301; HED Doc. Nos. 009544, 005752, 005174, and 012227], ODM (52% a.i. in MIBK) was administered in the feed at nominal concentrations of 0, 2, 20, or 200 ppm (analytically confirmed doses of 0, 0.57, 4.6, or 52 ppm of a.i., equivalent to 0, 0.027, 0.224 or 3.04 mg/kg/day, respectively, in males and 0, 0.036, 0.284 or 3.60 mg/kg/day, respectively, in females) to Fischer 344 rats (50 rats/sex/dose, an additional 5 rats/sex/dose were assigned to a ChE substudy) for 118 weeks. Plasma and erythrocyte ChE activities were determined after 4 and 118 weeks of treatment. After 4 weeks of treatment, the ChE substudy animals were sacrificed for determination of plasma, erythrocyte and brain ChE activities. At study termination (week 118), plasma, erythrocyte, and brain ChE activities were measured on randomly selected animals (5/sex/dose).

Treatment-related systemic effects were limited to high-dose males and females and consisted of changes in mean body weights, food consumption and absolute and relative organ weights. Body weights of high-dose animals were statistically significantly depressed at weeks 26 (males only), 52, 78, and 104. Mean body weights of high-dose animals progressively decreased during the study. At week 104 decreases of 17% were observed in males and 14%, in females. Despite the decreases in mean body weight, food consumption for high-dose males and females was statistically significantly increased at weeks 26, 52, 78 (females only) and 104. Changes in tissue weights consisted of increases in absolute brain and ovarian weights and relative brain weight. At the high-dose, absolute testes weights were increased to 120% of control values, while absolute ovarian weights may have been decreased to 32% of control value (neither was statistically significant and judged to be equivocal responses). Nominal, but not statistically significant, increases in retinal degeneration occurred in females, but not in males, at the high-dose.

Statistically significant inhibition of plasma, erythrocyte and brain ChE activities were observed after four and 118 weeks of treatment. After four weeks of treatment, plasma ChE activity was inhibited in mid-dose females (42%) and high-dose males (64%) and females (86%). At this same time point, erythrocyte ChE was inhibited in mid- and high-dose males (29% and 44%, respectively) and females (34% and 47%, respectively); and brain ChE activity was inhibited in low- mid- and high-dose males (11%, 51% and 89%, respectively) and females (6.2%, 49%, and 88%, respectively). After 118 weeks of treatment, plasma and erythrocyte ChE activities

were inhibited in mid- and high-dose animals, while brain ChE activity was inhibited at all dose levels. Plasma ChE activity was inhibited by 58% and 91% in mid- and high-dose, males, respectively, and 51% and 91%, in females, respectively. Erythrocyte ChE activity was inhibited by 54% and 83% in mid- and high-dose males, respectively, and 61% and 84% in mid- and high-dose females, respectively. Brain ChE activities were significantly inhibited at the low-dose (8.3% in males and 8.0% in females), mid-dose (53% in males and 50% in females), and high-dose (86% in males and 84% in females).

No treatment related neoplasia was observed in this study. ODM did not alter the spontaneous tumor profile in this study.

Because no NOEL was established for brain ChE activity, this study was initially graded as supplementary, pending results of a 90-day brain ChE study. The 90-day brain ChE study was found to be acceptable (see section j.3).

Based on the results of this study (decreases in body weights of 17% in males and 14% in females), the systemic LOEL was established at 52 ppm (3.04 mg/kg/day in males and 3.60 mg/kg/day in females). The systemic NOEL was established at 4.6 ppm (0.224 mg/kg/day in males and 0.284 mg/kg/day in females).

Based on the results of this study (inhibition of brain ChE by 8.3% in males and 8.0% in females), the ChE LOEL was established at 0.57 ppm (0.027 mg/kg/day in males and 0.036 mg/kg/day in females). The ChE NOEL was not established.

2) Oral (Feeding) Oncogenicity Study in Mice: In this study [MRID No.: 42576601, HED Doc No.: 010836], ODM (91.6 to 94.2%) was administered in the diet of CD-1 mice (50/sex/dose) at 0, 3, 15 or 50 ppm (0, 0.5, 2.3 or 7.8 mg/kg/day in males and 0, 0.6, 2.9 or 8.9 mg/kg/day in females) for 21 months. Organs and tissues were examined histologically for pathological changes, including tumors. Plasma, erythrocyte and brain ChE activities were determined after 12, 18 and 21 months of treatment.

Systemic toxicity was limited to animals treated at the mid- and high-dose levels. At the high-dose, the mean body weight of males was slightly, but significantly, decreased; the decreases, however, were not of biological importance (4% to 7%). An increased incidence of clonic convulsions in both sexes was observed at the high-dose. At the mid-dose level, increased incidence of inflammation, ulceration and acanthosis of the pinnae of the ears was observed in both sexes. Also seen at this dose level were histological changes in males, which consisted of vacuolation of the epithelial cells of the epididymis. No systemic toxicity was observed at the low-dose level.

Statistically significant inhibition of plasma, erythrocyte and brain ChE activities were observed during the study. At the low-dose level, plasma ChE activity was significantly inhibited in females by 21 to 22% after 12 and 18 months of treatment; males were unaffected at this dose level. Erythrocyte ChE activity in low-dose animals was significantly inhibited in males (9% to

17%) and in females (10% to 12%). Plasma ChE activity was inhibited at the mid-dose males (50 to 54%) and females (50 to 62%) and high-dose males (80 to 86%) and females (82 to 89%). Erythrocyte ChE activity was also significantly inhibited at the mid-dose (34 to 40% in males and 25 to 38% in females) and high-dose (39 to 45% in males and 39 to 48% in females) levels. Analysis of brain ChE activity at month 21 revealed statistically significant inhibition at the low-dose (11% in males and 17% in females), mid-dose (51% in males and 48% in females) and high-dose (73% in males and 63% in females) levels.

No compound-induced carcinogenic response was observed under the conditions of the study. Adequate dose levels were used to assess the carcinogenic potential of ODM.

Based on the results of this study (increased incidence of cytoplasmic vacuolation in the epididymides in males and increased inflammation, ulceration and acanthosis of the pinnae of the ears in both sexes), the LOEL for systemic toxicity was established at 15 ppm (2.3 mg/kg/day in males, and 2.9 mg/kg/day in females). The NOEL for systemic toxicity was established at 3 ppm (0.5 mg/kg/day in males and 0.6 mg/kg/day in females).

Based on the results of this study (inhibition of brain and erythrocyte ChE activity in both sexes and plasma ChE activity in females), the ChE LOEL was established at 3 ppm (0.5 mg/kg/day in males and 0.6 mg/kg/day in females). **The ChE NOEL was not established.**

3) Chronic Study in the Dog: In another chronic toxicity study [MRID Nos. 00151805, 41082201, 41980801, 43454201. HED Doc. Nos. 009544, 005752, 005174, and 012227], ODM (51.1% a.i. in MIBK) was administered to six Beagle dogs per sex per group by gavage (stomach tube) at dose levels of 0, 0.0125, 0.125 or 1.25 mg/kg/day (corrected for % a.i.) for 12 months. Plasma and erythrocyte ChE activities were determined at weeks -2, -1, 3, 6, 13, 26, 39 and 52. Brain ChE activity was determined in the bulbous olfactorious at termination of the study. Histological examinations were conducted initially on high-dose and control dogs, but in supplemental data submissions, additional histological studies were submitted on the remaining dose levels.

Evaluation of ChE activities during the study revealed inhibition of plasma, erythrocyte and brain activities. Plasma ChE was inhibited only at 1.25 mg/kg/day, with decreases of 38% to 48% in males and 40 to 44% in females from weeks 6 to 52. At 0.125 mg/kg/day, erythrocyte ChE was statistically significantly inhibited at week 26 (20% in males and 25% in females) and non-significantly inhibited at week 52 (11% in males and 15% in females). At the high-dose level, significant inhibition of erythrocyte ChE activity was noted from weeks 6 to 52 in males (32% to 45%) and weeks 13 to 52 in females (47% to 50%). Brain ChE was statistically significantly inhibited in mid-dose females (12%) and high-dose males (45%) and females (46%).

There were nominal increases in ovarian weight of 100% and 50% in low- and mid-dose females, respectively; ovarian cysts were observed at microscopic examination. Other histological findings included fatty change of the adrenal cortex and alveolar edema of the apical portion of

one of the pulmonary lobes.

Based on the results of this study (inhibition of erythrocyte ChE in males and females and brain ChE in females), the ChE LOEL was established at 0.125 mg/kg/day. The ChE NOEL was established at 0.0125 mg/kg/day.

d. Developmental Toxicity

Developmental studies are designed to identify potential adverse effects in developing organisms resulting from the mother's exposure to the test material during pre-natal development. Acceptable data from rat and rabbit developmental studies satisfy the data requirements for guideline 83-3(a) and (b).

1) Developmental Toxicity Study in the Rat: In a developmental toxicity study [MRID Nos. 00146812, 00158342; HED Doc. Nos. 012220, 004822, 005585, also published in Fundamental and Applied Toxicology 14, 131-143(1990)] in Charles River COBS CD rats, ODM (90.6%) was administered by gavage at doses of 0, 0.5, 1.5 or 4.5 mg/kg/day to about 45 presumed pregnant rats per group from gestation day (GD) 6 through 15. The study was divided into three phases.

Phase I: Pregnant rats, 5 per group, were euthanized on GD 16 for determination of maternal plasma, erythrocyte and brain ChE activities.

Phase II: Pregnant rats, 28 per group, were euthanized on GD 20 and corpora lutea, implants, implantation sites were counted, and fetuses examined for external, visceral and skeletal anomalies. Plasma, erythrocyte and brain ChE were determined on 10 dams per group. Brain ChE was determined in 20 fetal brains per group, randomly selected across litters.

Phase III: Pregnant rats, approximately 9 to 12 per group, were allowed to deliver their pups and then examined for nesting behavior and parturition, including premature or prolonged labor and dystocia. On day 4 of lactation, litters were reduced to 5 per sex per group. Litters were weighed on lactational day 0, 4, 7, 14 and 21. During this period, dams were evaluated in a litter retrieval test. In addition, one pup per sex per group from 10 litters was randomly selected and subjected to a battery of developmental indices (pinnae unfolding, incisor eruption, eye opening, testicular descent, vaginal patency), reflex (visual placement, negative geotaxis, auditory startle reflex, olfactory orientation, surface righting, air righting, sensory), maze learning and open field activity (horizontal and vertical activity, total distance traveled, revolutions, rest time and total excretions).

Maternal toxicity was demonstrated at the high-dose level and consisted of slight, but statistically significant, decreases in mean body weight of 2.6% on GD 12 and 3% on GD 12. A statistically significant decrease in mean body weight gain (11.5%) was observed from GD 6 to 20. Food consumption was decreased by 8% on GD 8 and 6% on GD 12. Clinical signs (transient tremors) were also observed in essentially all (98%) of the high-dose dams.

Maternal plasma, erythrocyte and brain ChE activities were evaluated on GD 16 and 20. On GD 16, ChE activity was inhibited at the low-, mid- and high-dose levels by 30%, 54%, and 72%, respectively, for plasma and 21%, 52%, and 68%, respectively, for brain. Erythrocyte ChE was inhibited by 37% at the mid-dose level and by 56% at the high-dose level. On GD 20, marked inhibition of brain ChE was still apparent at the low- (19%), mid- (38%) and high- (54%) dose levels. Erythrocyte ChE was inhibited at the high-dose level by 40%, while plasma ChE activities were unaffected.

No developmental toxicity or inhibition of fetal brain ChE was observed at the highest dose tested. Further, no effects were observed in any of the developmental indices, reflex evaluation, maze learning or open field activity at any dose level.

Based on the results of this study (inhibition of plasma ChE by 30% and brain ChE by 21% on GD 16), the maternal LOEL was established at 0.5 mg/kg/day. The maternal ChE NOEL was not established (less than 0.5 mg/kg/day, low dose tested).

The LOEL for developmental toxicity was not established (greater than 4.5 mg/kg/day); the NOEL for developmental toxicity was established at 4.5 mg/kg/day, the highest dose tested. No effects were noted in fetal brain ChE activities at GD 20.

2) Developmental Toxicity Study in the Rabbit: In another developmental toxicity study [MRID Nos. 00146989, 00153606, 42859901; HED Doc. Nos. 003844, 004437, 011394, 012220], ODM (53.5% a.i. in MIBK) was administered by gavage at 0, 0.1, 0.4, or 1.6 mg/kg/day (0, 0.05, 0.2 or 0.8 mg a.i./kg/day) to 17 presumed pregnant American Dutch rabbits from GDs 7 to 19. Rabbits were weighed on GDs 0, 7, 10, 14, 17, 21 and 28. At GD 28, rabbits were sacrificed, and corpora lutea, implantation sites, and live and dead implants were counted. In a separate ChE substudy, plasma, erythrocyte and brain ChE activities were determined on five randomly selected does per group at GDs 20 and 28; the rabbits were dosed by gavage at 0, 0.05, 0.2 or 0.8 a.i. mg/kg/day. All fetuses were examined for external, visceral and skeletal abnormalities.

Doses for the main study were selected, based on the results of a range-finding study in which rabbits (2 to 3/dose) were administered ODM at 0.05, 0.25, 0.5, 1.5, 3.0, or 6.0 mg a.i./kg/day from GD 6 to 19. Observed clinical signs included mortality in all three animals dosed at 6 mg/kg/day and one out of three animals dosed at 3 mg/kg/day. The two surviving animals at 3 mg/kg/day lost considerable of body weight. No post-implantation losses were observed at 0.5 mg/kg/day and lower doses, while post implantation losses at doses of 1.5, 3.0, or 6.0 mg/kg/day were 42, 83 and 100%, respectively. Based on the results of this range-finding study, doses of 0.05, 0.2 or 0.8 mg a.i./kg/day were selected for the main study.

In the definitive study, clinical signs of toxicity included loose stools in 5/17 dams dosed at 0.2 mg/kg/day and 8/17 dams dosed at 0.8 mg/kg/day, these effects were judged to be of equivocal biological significance. No treatment-related changes were seen in either the maternal body weight or body weight gain during the gestation period.

Litter size, fetal viability and weight were not affected at any dose level. Soft tissue abnormalities occurred in control and high-dose animals with similar frequencies and with no dose-response relationship. No developmental toxicity was observed at the skeletal examination of the fetuses. Slight increases in incomplete ossification of the metacarpals were observed at all dose levels (14.1 to 17.6% of treated fetuses affected compared to 4.2% for control fetuses). This finding, however, was considered to be equivocal and incidental to the study, since this finding is a variable parameter and lacked a clear dose-response relationship in this study.

Maternal ChE activities were determined on GDs 20 and 28 (9 days post-dosing). No inhibition of plasma ChE was noted at any time period or dose level. At the high-dose level, erythrocyte and brain ChE were statistically significantly inhibited by 43% and 21%, respectively, on GD 20. On GD 28, plasma, erythrocyte and brain ChE activities of the treated dams were comparable to control values.

Based on the results of this study (inhibition of erythrocyte ChE by 43% and brain ChE by 21% on gestation day 20), the maternal LOEL was established at 0.8 mg/kg/day, The maternal NOEL was established at 0.2 mg/kg/day.

The developmental toxicity LOEL was not established (greater than 0.8 mg/kg/day), the NOEL was established at 0.8 mg/kg/day.

e. Reproductive Toxicity

The objective of multigeneration reproduction studies is to determine the general effects of a test material on overall reproductive capability of parental animals and the growth and development of their offspring. Acceptable data from two rat studies satisfy the requirements for guideline 83-4.

1) Reproductive Toxicity Study in the Rat: In a two-generation, two litter reproductive toxicity study [MRID No. 00260513 and addendum 00256926; HED Doc. No. 005716], ODM (52.5% in MIBK) was administered to Wistar [Bor:WISW(SPF-Cpb)] rats (20 females/dose and 10 males/dose) at dietary levels of 0, 1, 10, or 50 ppm (0, 0.05, 0.5, or 2.5 mg/kg/day, respectively; unadjusted for percent purity or for degradation). Animals were treated continuously from 42 to 48 day old F_0 generation rats through the successive generations.

Parental systemic toxicity was observed at 10 ppm and higher dose levels. At 10 and 50 ppm, parental toxicity consisted of statistically significant decreases in mean body weight and body weight gain of F_0 males and F_1 males and females at termination. At 50 ppm, body weight gain of F_0 and F_1 females was significantly decreased during gestation. Cholinergic signs (slight tremor) were observed at 50 ppm until week 14 for F_0 animals. Decreased pup weight during lactation was observed in the offspring.

The fertility index (expressed as the percent of the ratio of number of pregnant females to the number females mated) and viability index (expressed as the percent of the ratio of the number of

pups alive after 5 days to the number pups born) showed treatment-related changes. The fertility index was nominally lower in the mating for the F_{1a}, F_{1b} and F_{2b} litters. None of these values was statistically significant and only in the high-dose group was the value lower than the historical control range. Litter sizes at birth were statistically significantly lower at 50 ppm (7.9 to 8.3 pups/litter compared to control values of 10.8 to 11.1 pups/litter) for the F_{1a}, F_{1b}, F_{2a} and F_{2b} litters, resulting in a nominal reduction in the viability index.

At terminal sacrifice, decreased absolute testis weight was observed in high-dose males. Histopathological examination revealed vacuolization of the epithelial cells in the epididymal corpus, in high-dose males as well as those in the mid-dose group. No reproductive toxicity was observed at 1 ppm.

The parental systemic toxicity LOEL was established 10 ppm (0.5 mg/kg/day), based on decreased male and female body weight during entire study and reduced gestation body weight for females. The NOEL was established at 1 ppm (0.05 mg/kg/day)

The reproductive toxicity LOEL was established at 10 ppm (0.5 mg/kg/day), based on decreased absolute testis weight and increased incidence of vacuolization of the epithelial cells in the epididymal corpus. The NOEL was established at 1 ppm (0.05 mg/kg/day).

The offspring LOEL was established at 10 ppm (0.5 mg/kg/day), based on decreased viability index and decreased pup weight during lactation. The NOEL was established at 1 ppm (0.05 mg/kg/day).

2) Reproductive Toxicity Study in the Rat: In another two-litter, two-generation reproductive toxicity study [MRID No. 41461901; HED Doc. No. 012223], Sprague-Dawley rats were administered ODM (50% a.i. in MIBK) at dietary levels of 1, 3, 9, or 50 ppm (0, 0.043, 0.13, 0.38, 2.1 mg/kg/day, respectively). Additional groups were fed diets containing 50 ppm (2.1 mg/kg/day) of ODM, technical (94.6%), or 50 ppm of MIBK (0.0 mg/kg/day). MIBK was included to evaluate whether the observed effects (epididymal vacuolation) were associated with ODM and not the vehicle.

Parental systemic toxicity was observed in animals in both 50 ppm groups. Mean body weight was slightly reduced in F_1 males (95% to 96% of control values) and in gestating and lactating females of both generations (25% to 90% of control values).

Decreased male and female fertility of non-defined origin was observed in the F_0 and F_1 generations. The respective fertility indices for the F_{1a}, F_{1b}, F_{2a} and F_{2b} litters were 40%, 36%, 63% and 33% for the 50 ppm of the 50% concentrate and 57%, 39%, 43% and 20% for the 50 ppm of technical ODM. The incidence of epididymal vacuolation was 100% in the F_0 and F_1 males, the lesion was graded as moderate to marked. Absolute testes weights (89% to 96% of controls) and ovarian weights (76% to 86% of controls) were reduced. Dams with decreased numbers of corpora lutea (16% to 35% reduction from control values) and with nominally increased estrous cycle length (mean number of cycles per 2 week period, 65% to 85% of control

values) were seen at the high-dose level. Possible effects on fertility at 9 ppm were not statistically significant nor considered to be biologically significant effects.

For the offspring, systemic toxicity was observed at 50 ppm, and consisted of decreased litter size at birth and decreased pup weight during lactation. No systemic toxicity was observed in offspring dosed at 1, 3 or 9 ppm.

Parental ChE inhibition was observed at 1 ppm and higher. At 1 ppm, brain ChE was inhibited 8% in males and 7% to 11% in females. There was progressively more inhibition of brain ChE with increasing dose levels (3 ppm: 16% to 17% in males and 20% to 21%, females; 9 ppm: 40% in males and 42% to 46%, females; 50 ppm (both groups): 75% to 78% in males and 76% to 79% in females). Erythrocyte ChE was inhibited at 1 ppm (7% to 8% in males and 7% to 10% in females), 3 ppm (12% to 20% in males and 16% to 26% in females), 9 ppm (29% to 38% in males and 36% to 41% in females), and 50 ppm (both groups (48% to 52% in males and 48% to 52% in females). Plasma ChE was not inhibited at 1 ppm, and at the 3 ppm dose level, 2 of 12 sampling periods were significantly inhibited (pre F1a-18% and pre F2a-29%) in males and females, but these may have been random variation. At 3 ppm, plasma ChE activity was inhibited 12% to 26% in males and females, at 9 ppm, 29% to 41% in males and females, and at 50 ppm (both groups), 54% to 85% in males and females.

Inhibition of ChE in offspring was observed at 9 ppm, with plasma erythrocyte, and brain ChE inhibited 24% to 29%, 10% to 14%, and 8% to 12%, respectively. There were no apparent sex difference.

Based on the results of this study (decreases in male fertility and female fertility of unknown origin in P and F1 generations), the parental systemic toxicity LOEL was established at 50 ppm (2.1 mg/kg/day). The NOEL for parental systemic toxicity was established at 9 ppm (0.38 mg/kg/day).

Based on the results of this study (inhibition of brain ChE by 7% to 11% and erythrocyte ChE by 10% to 75%), the parental ChE LOEL was established at 1 ppm (0.043 mg/kg/day), the lowest dose tested. The parental ChE NOEL was not established.

The offspring LOEL was established at 50 ppm (2.1 mg/kg/day), based on decreased litter size at birth and decreased pup weight during lactation. The offspring NOEL was established at 9 ppm (0.38 mg/kg/day)

Based on the results of this study (inhibition of plasma, erythrocyte, and brain ChE activities of 24% to 29%, 10% to 14%, and 8% to 12%, respectively, with no sex difference), the offspring ChE LOEL was established at 9 ppm (0.38 mg/kg/day); the NOEL was established at 3 ppm (0.13 mg/kg/day).

f. Mutagenicity

The purpose of mutagenicity tests is to assess the potential of the test substance to alter genetic material. Twelve acceptable mutagenicity studies on ODM were reviewed and summarized

1) Gene Mutations

***Salmonella typhimurium* reverse gene mutation assay** [MRID No. 00146091; HED Doc. Nos. 005174, 005752]: The test was positive in *S. typhimurium* TA1535 and TA100 with reproducible and concentration-dependent increases in mutant colonies at 6000-12,000 µg/plate without S9-activation and 3000-12,000 µg/plate with S9-activation.

Mouse lymphoma L5178Y TK$^{+/-}$ forward gene mutation assay [MRID No. 00146102; HED Doc. No. 005174]: The test was positive; dose-related increases in the mutation frequency (MF) were seen at 500-1500 nL/mL without S9-activation (assumed to be equivalent to ≈500-1500 µg/mL) and at 2-50 nL/mL with S9-activation (≈2-50 µg/mL)

***In vivo* mouse spot test** [MRID No. 42136901; HED Doc No. 009402]: The test was positive for the induction of somatic cell mutations following the intrauterine exposure of embryos to a maternal dose of 20 mg/kg. In this study , C57BL/6J female mice were mated to "T-stock" males and administered single oral gavage doses of 5, 10 or 20 mg/kg ODM (Trial 1) or 12, 16 or 20 mg/kg (Trial 2) on gestation day 10. Deaths (1-5%) and other toxic signs consistent with cholinergic effects were seen at 20 mg/kg; cholinergic effects were also apparent at 16 mg/kg but not at ≤12 mg/kg. The reduction in the number of females bearing live litters seen at the highest dose tested parallels the findings from reproduction/ fertility studies (see MRID Nos. 41461901, 00260513, 40988001) showing decreased litter size and/or number. In the mutation phase of the study, significant ($p \leq 0.05$) and reproducible increases in mutation were obtained at 20 mg/kg. The data further suggest that the response was dose-related with an ≈3.7-fold (but not statistically significant) increase in mutation at 12 mg/kg.

2) Chromosomal Aberrations

***In vitro* Chinese hamster ovary (CHO) cell chromosome aberration assay** [MRID No. 40658502; HED Doc. No. 007780]**:** The test was positive at 0.5 and 1.0 µL/mL (≈500-1000 µg/mL) without S9-activation and at S9-activated doses of 2.5 and 5.0 µL/mL (≈2500 and 5000 µg/mL). Severe cytotoxicity and mitotic suppression was noted at higher nonactivated levels.

In vitro Chinese hamster ovary (CHO) cell chromosome aberration assay [MRID No. 40534501; HED Doc. No. 009544]: The test was positive; significant and dose-related clastogenic effects were observed at 1000-2000 µg/mL without S9-activation. Significant effects were also noted at 5000 µg/mL with S9-activation. Severe cytotoxicity and mitotic suppression was apparent at higher nonactivated concentrations.

***In vivo* bone marrow cytogenetic assay** [MRID Nos. 41236301/41667701; HED Doc Nos. 007881/008973]**:** The assay was negative in male and female Chinese hamsters receiving a single

oral gavage administration of 40 mg/kg (only dose tested). Toxic signs consistent with ChE inhibition were noted, however, there was no evidence that ODM reached the target tissue.

Dominant lethal assay [MRID No. 40628201; HED Doc. Nos. 006590 and 006782]**:** Findings were initially considered inconclusive but upon submission of additional data, it was concluded that ODM was negative in CD-1 male mice up to the Highest dose tested (4.5 mg/kg administered as a single intraperitoneal injection). Overt toxicity (lethargy and cowering) but no evidence of test material/target cell interaction were recorded at the Highest dose tested.

Dominant lethal plus assay [MRID No. 40988001; HED Doc. No. 007494]**:** The test was negative for dominant lethal effects in the germinal cells of male Sprague-Dawley rats administered 0.15-5.0 mg/kg ODM by oral gavage for 5 consecutive days premating. Death and signs of a cholinergic response were reported at the Highest dose tested; decreased sperm motility was also seen at 5.0 mg/kg. It should be noted that effects on sperm motility were not seen in the other dominant lethal assays or in the reproduction, fertility or sperm motility studies. Thus, the effects on sperm in this study have not been confirmed.

3) Other Mutagenic Mechanisms

Unscheduled DNA synthesis (UDS) in primary rat hepatocytes [MRID No. 40658503; HED Doc. No. 007780]: The test was negative up to the highest dose tested (1.0 µL/mL, equivalent to ≈1000 µg/mL); higher concentrations (≈2.0 µL/mL) were cytotoxic.

Sister chromatid exchange (SCE) in CHO cells assay [MRID No. 40658501; HED Doc. No. 007780]: The test was positive with significant increases in SCE induction at all assayed levels (0.08-0.6 µL/mL without S9-activation or 0.6-5 µL/mL with S9-activation, equivalent to ≈80-600 µg/mL without-S9-activation or ≈600-5000 µg/mL with S9-activation). The response was clearly dose-dependent in the presence of S9-activation and severe mitotic delay occurred at ≥0.5 µL/mL without S9-activation (≈500 µL/mL).

***In vitro* alkaline elution assay in CHO cells** [MRID No. 43776101; HED Doc. No. 012198]**:** The test was positive; ODM caused reproducible and dose-related increases in DNA single strand breaks at 2000-5000 µg/mL without S9-activation and 500-5000 µg/mL with S9-activation.

***In vitro* alkaline elution assay in primary rat testes cells** [MRID No. 43776103; HED Doc. No. 012198]**:** The test was positive; reproducible and dose-related increases in DNA single strand breaks were noted at 2000-5000 µg/mL without S9-activation; the assay was not performed in the presence of exogenous metabolic activation.

4) Summary for mutagenicity studies: In its final report (May 7, 1998, HED Doc No.: 012606), the Health Effects Division, Identification Assessment Committee (HIARC) concluded the following:

"Findings from the acceptable genetic toxicology studies indicated that ODM is mutagenic in bacteria and mutagenic and clastogenic in cultured mammalian cells. It also induced mitotic suppression and SCEs in several mammalian cell lines and caused DNA single strand breaks in cultured CHO cells and primary rat testes cells. The results further indicate that ODM is active *in vitro* in both the presence and absence of S9-activation. The large body of evidence showing that ODM is genotoxic in a wide variety of *in vitro* test systems submitted by the registrant is also supported by studies in the open literature. ODM was, however, not carcinogenic in chronic rat or mouse feeding studies or clastogenic in the *in vivo* bone marrow cells of treated Chinese hamsters.

In contrast, Pandita (Mutat. Res. 124:97-102, 1983) reported that the intraperitoneal injection of 10-18 mg/kg ODM once daily for 2 days produced dose-related and significant increases in micronucleated polychromatic erythrocytes recovered from the bone marrow of Swiss albino mice. ODM also induced somatic cell mutations at 20 mg/kg in the *in vivo* mouse spot test. The data from this study showing that ODM penetrated the placental barrier and caused genetic damage taken in conjunction with the consistent finding of reduced testicular and/or ovarian weights in the reproduction studies and possible adverse effects on sperm motility suggest a potential concern for heritable effects. There is also clear evidence from the *in vitro* alkaline elution assay that ODM caused DNA single strand breaks in rat testes cells.

The issue as to whether ODM induces DNA single strand breaks in rat testes cells *in vivo* has, however, not been resolved since the study addressing this endpoint was classified as Unacceptable. Although ODM was negative in the two acceptable *in vivo* dominant lethal assays, it is not clear whether a potentially genotoxic concentration of ODM was available to interacted with gonadal DNA since the doses used were $\leq$5 mg/kg. We based this hypothesis on the data from the metabolism study (see sec g, metabolism study) in rats showing that low doses of ODM (1 mg/kg) are biotransformed but that biotransformation may be saturated at high doses (20 mg/kg). The results indicating that a marked increased in excretion of the unmetabolized parent (59 or 74% in males or females, respectively) in the urine in conjunction with a marked decline in the excretion of metabolites compared to the corresponding values for males and female rats receiving 1 mg/kg (excretion of unmetabolized parent: 34-43% in males and 47-55% in females) strengthens the Committee's position.

Despite the lack of *in vivo* confirmation of DNA damage in male germinal cells, the Committee concluded that the weight-of-evidence argues for potential adverse heritable effects. Based on the above deliberations, the Committee initially considered requiring a mouse specific locus test since ODM was positive for the indicators of germ cell genotoxicity: *in vitro* and *in vivo* mutagenicity, distribution of the test material to the gonads (see sec. g, metabolism study), reduced testicular and/or ovarian weights and decreased size and/or number of litters in the reproduction studies. The Committee, nevertheless, concluded that additional testing to investigate possible genetic damage leading to heritable effects was not warranted at this time. The HIARC Identification Committee recommend, however, that the concern for possible adverse heritable effects be included as an Uncertainty Factor in setting the RfD for ODM."

g. Metabolism

The purpose of general metabolism testing is to obtain information on the absorption, distribution, biotransformation, and excretion of the test substance as a function of dose.

In a metabolism study [MRID No.: 41310201; HED Doc No.: 008046], rats were dosed with ^{14}C-1-ethylene-labeled ODM (^{14}C-ODM) at a single at dose 1 mg/kg, either intravenously (iv) or orally (po), a single oral dose at 20 mg/kg, or with 14 daily oral doses of unlabeled ODM at 1 mg/kg/day followed by a single oral dose of ^{14}C-ODM at 1 mg/kg.

The results of this study show that ^{14}C-ODM was rapidly absorbed, extensively metabolized, and rapidly excreted. Over a 3-day period, most (90-108%) of the administered dose was excreted. The radioactivity was recovered almost entirely in the urine (89 to 105% of the administered dose), while feces and expired CO_2 accounted for 0.2 to 2.9% and 0.1% of the administered dose, respectively. There was no indication of bioaccumulation in any tissue or organ

The identification of major urinary and fecal metabolites were determined for each treatment group. Analysis of the urinary radioactivity revealed that most of administered ^{14}C-ODM was not metabolized. The respective percents for males and females of unmetabolized ODM were 43% and 47% for the 1 mg/kg, iv group; 38% and 47% for the 1 mg/kg, po group; 34% and 55% for the repeat, 1 mg/kg/day, po group; and 59% and 74% for the 20 mg/kg, po group. Two major metabolites and three minor ones were also identified. One major metabolite was identified as 2-(ethylsulfinyl)-1-(methylsulfinyl) ethane, and accounted for 18% to 21% of the administered dose at 1 mg/kg, iv; 24% to 25%, at 1 mg/kg, po; 15%, at 15 x 1 mg/kg/day, po; and 5% to 6%, at 20 mg/kg, po. The second major metabolite was identified as 2-(ethylsulfonyl)-1-(methylsulfinyl) ethane; this metabolite accounted for 11% to 19% of the administered dose at 1 mg/kg, iv; 16% to 20%, at 1 mg/kg, po; 12% to 23%, at 15 x 1 mg/kg/day, po; and 6% to 19%, at 20 mg/kg, po. One minor metabolite (as a percent of the administered dose for both males and females) was identified as ODM sulfone and was present at 1.7% to 3.4% of the total administered dose at 1 mg/kg, iv; 1.6%, at 1 mg/kg, po; 2.4% to 2.6%, at 15 x 1 mg/kg/day, po; and 2.6% to 3.9%, at 20 mg/kg, po. Two other minor metabolites were identified as desmethyl ODM and desmethyl ODM sulfone and were detected only in the 20 mg/kg, po, group at 2.6% to 3.1% and 1.0 to 3.1%, respectively. Primary fecal metabolites included unmetabolized ODM (0.2%), ODM sulfide (0.8%) and ODM sulfone (0.2%).

The differences in the metabolic profiles suggests that the biotransformation may be saturated at high doses. The results indicate that at 20 mg/kg a marked increase in urinary excretion of unmetabolized parent compound (59 to 74%) in conjunction with a marked decline in the urinary excretion of metabolites compared to the corresponding values for males and female rats receiving 1 mg/kg (excretion of unmetabolized parent: 34 to 55%).

h. Neurotoxicity

Neurotoxicity studies are designed to identify acute, subchronic and/or delayed neurotoxic effects of chemicals. While all chemicals are evaluated for major neurobehavioral and neuropathological effects in the acute and subchronic neurotoxicity screening batteries in rats, selected classes of chemicals (organophosphates) are also evaluated for delayed neurotoxicity in adult hens.

1) Acute Delayed Neurotoxicity Study in the Hen: In this study [MRID Nos. 00146105, 40860001; HED Doc Nos: 0005174, 0005752, and 009342], ODM (54% concentrate in MIBK) was administered by gavage in a single dose of 200 mg/kg (approximate LD_{50}) to 23 White Leghorn hens. ODM-treated hens were protected by atropine (50 mg/kg, i.m.) and (2-PAM, 31 mg/kg, i.m.) 30 and 45 minutes
after the dose of ODM. Hens surviving to 21 days were again dosed and protected identically as before and observed for an additional 21 days (42 days in all) for clinical signs. Body weights were determined and perch tests were performed twice weekly. Eight negative (untreated) control hens, eight atropine/2-PAM control hens and eight triorthocresyl phosphate (TOCP, 556 mg/kg) positive control hens were included in the study. Complete gross necropsy was conducted and histological examination of the sciatic nerve (tibial and peroneal branches), spinal cord (cervical, thoracic and lumbar) and brain (mid-brain, brain-stem and cerebellum) was performed on each bird.

Clinical signs observed during the study included lethality in eight of 23 the ODM-treated hens; all hens showed signs of ChE inhibition. Statistically significant body weight decreases of about 10% were reported; however, these body weight decreases could not be verified by supplemental data submissions because the bird weights were not obtained at the same time. There were no significant differences from controls in the perch test.

A biologically significant increase in the incidence of neurological lesions was seen compared with the negative control and the antidote treated group. A slight increase in the incidence and/or severity of degeneration was seen in several nerve sites. The incidence of degeneration (digestion chambers) was 100% in cervical spine and thoracic spine (compared with 75% and 63%, respectively for the negative control), 93% in the lumbar spine (50% for negative control), 33% in the sciatic nerve (13% for the negative control) and 40% in the tibial nerve (0% for the negative control). Axonal swelling also was increased in the cervical spine (27%) and thoracic spine (47%). In addition, the incidence and/or the grade was increased for macrophage and lymphocyte accumulation in the cervical spine, thoracic spine and lumbar spine. The TOCP treated hens showed typical lesions.

Taken as a whole, the data suggests that ODM caused biologically significant increases in the incidence of neurological lesions compared with the incidence of lesions in the negative control and antidote control groups.

2) Subchronic (90-Day) Delayed Neurotoxicity Study in the Hen: In this study [MRID No. 41348201; HED Doc No: 009542, 012031], ODM (92.6%) was administered by gavage (in water) to groups of 12 Leghorn hens at 0, 1, 5 or 10 mg/kg/day, 5 days/week, for 13 weeks. A

TOCP positive control group was also included in the study. Hens were observed for adverse clinical signs, mortality, ataxia, and whole blood ChE; gross and histological examination were also performed. Two range-finding studies were also submitted, which indicated that mortality, body weight decrement and ChE inhibition occurred within 5 days at a dose level of 20 mg/kg/day. Thus, 20 mg/kg/day was considered too high a dose level for the 90-day study.

Systemic toxicity was observed during the 90-day study. Although no treatment-related clinical signs were observed, one death at 10 mg/kg/day may have been test material related. Body weights were decreased 5% and 12% from control at 5 and 10 mg/kg/day, respectively. Body weight gains decreased 42% and 92% from control at 5 and 10 mg/kg/day, respectively. Although body weights and body weight gains appeared to show a decreasing trend at 5 and 10 mg/kg/day, neither was statistically significant at termination of the study.

ChE activity was statistically significantly inhibited at 5 mg/kg/day (35% at dosing day 4, 34% at day 25 and 16% at day 88) and at 10 mg/kg/day (38% at day 4, 42% at day 25 and 16% at day 88).

Pathological evaluations revealed slightly increased severity of neurological lesions, but the severity grade increase was equivocal, with no corresponding increase in incidence of the lesion. Although a slightly higher dose level could have been used, the study is considered adequate to test for neurotoxicity in the hen.

The TOCP positive control group showed ChE inhibition, body weight loss, ataxia and histopathology of the brain, sciatic nerve and spinal cord.

Based on the results of this study (inhibition of whole blood ChE and a decreasing trend in body weight), The LOEL was established at 5 mg/kg/day. Microscopic neurological lesions did not appear to be induced by treatment. The NOEL was established at 1 mg/kg/day.

3) Acute Neurotoxicity Screening Battery in the Rat: In an acute neurotoxicity study [MRID No.: 43929901; HED Doc No. 012212], Sprague-Dawley Crl:CD^{R}(SD)BR strain rats (main study: 12/sex/dose; ChE substudy: 10/sex/dose/time point) were gavaged with ODM (50% concentrate in MIBK) at doses of 0, 2.5, 10 or 50 a.i. mg/kg. For neurobehavioral evaluations, animals were assessed for performance in the Functional Observational Battery (FOB) and motor activity at the peak time-of-effect (1.5 to 2.25 hours post-dosing) and at days 7 and 15. Plasma, erythrocyte and brain ChE activities were measured at the peak time of effect and on days 7 and 15.

Survival, body weights and food consumption were all affected at the high-dose level. High mortality (50%) was observed in this group, surviving animals had decreased body weight at days 7 (14% in males and 8% in females) and 14 (9% in males and 4% females). Food consumption was also greatly reduced (35% in males and 21% in females) for days 0 to 7.

Neurobehavioral toxicity was observed in the mid- and high-dose groups. At the mid-dose level, tremors, ataxic gait, decreased number of rearings, pinpoint pupils, abnormal visual placement, decreased defecation, absent tail pinch response, decreased body temperature and decreased motor activity were observed in both males and females. At the high-dose level, many additional FOB parameters were observed at 50 mg/kg.

Erythrocyte and brain ChE activities were inhibited at all three dose levels, while plasma ChE inhibition was observed only at the mid- and high-dose levels. On day 0 (peak time-of-effect) statistically significant inhibition of ChE activity was observed at the low-dose (erythrocyte ChE: 38% in males and 30% in females), mid-dose (plasma: 83% in males and females; erythrocyte: 49% in males and 47% in females; brain: 83% in males and 80% in females) and high-dose (plasma: 76% in males and 90% in females; erythrocyte: 49% in males and 52% in females; brain: 92% in males and females). At day 7, statistically significant decreases in ChE activity were observed in the brain at the low-dose (11% in males and 12% in females), mid-dose (20% in males and 23% in females) and high-dose (not measured in males and 45% in females). At day 7, erythrocyte ChE activities were comparable to control values in low-dose males and females and mid- and high-dose females; erythrocyte ChE activity was inhibited by 19% in mid-dose males and was not determined for high-dose males. On day 15, plasma ChE was significantly inhibited by 45% in high-dose males; plasma and erythrocyte ChE activity for other dose groups were comparable to control values. Brain ChE activity was still markedly inhibited at day 15 in low-dose (9% in males and 8% in females), mid-dose (16% in males and 15% in females) and high-dose (32% in males and 33% in females) animals.

Based on the results of this study (cholinergic signs of toxicity), the LOEL for systemic toxicity was established at 10 mg/kg. The NOEL was established at 2.5 mg/kg.

The LOEL for ChE inhibition was established at 2.5 mg/kg (Lowest dose tested) based on inhibition of brain ChE activity (9 to 11% in males and 8 to 12% in females). The NOEL was not established.

4) Subchronic (90-Day) Neurotoxicity Screening Battery in the Rat: In a subchronic neurotoxicity study [MRID No.: 44189501; HED Doc No. 012212], Sprague-Dawley rats (main study: 12/sex/group; ChE substudy: 10/sex/group/time period) were dosed ODM (50% concentrate in MIBK) for up to 13 weeks at 0, 1, 10 or 80 ppm (0, 0.062, 0.62, and 5.4 mg/kg/day in males and 0, 0.074, 0.75 and 6.6 mg/kg/day in females). Two additional groups of animals (10/sex/dose/time period), dosed at 0.1 or 0.3 ppm (0.0060 or 0.018 mg/kg/day in males and 0.0073 or 0.022 mg/kg/day in females), were assigned to the ChE substudy only. For main study animals neurobehavioral assessments (FOB and motor activity) were made at pretest and on weeks 4, 8 and 13. ChE substudy animals were sacrificed at weeks 4, 8 and 13 for determination of plasma, erythrocyte and brain ChE activities.

Systemic and neurobehavioral toxicity were observed at 80 ppm. Mean body weights were decreased up to 16% in males and 7% in females. Clinical signs included tremors, aggressive behavior, and fur staining; no deaths occurred during the study. Results of the FOB evaluation

revealed decreased hindlimb grip strength in high-dose males and females, and a slight decrease in body temperatures in mid- and high-dose females. Motor activity was not affected by treatment. No histopathological effects could be attributed to treatment.

ChE activities were significantly inhibited in males and females dosed at 10 and 80 ppm; at 1 ppm and lower plasma, erythrocyte and brain ChE activities were not significantly different from the control values. During the study, animals dosed at the 10 ppm had plasma ChE activity was inhibited by 32% to 39% in males and 49% to 58% in females; at 80 ppm, activities were inhibited by 49% to 58% in males and 71% to 78% in females. Erythrocyte ChE activities were inhibited by 17% to 35% in males and 19% to 35% in females at the 10 ppm dose level and 36% to 59% in males and 39% to 51% in females at the 80 ppm dose level. For males, brain ChE activity was inhibited 50% to 53% at 10 ppm and 77% to 78% at 80 ppm, and for females, 49% at 10 ppm and 77% to 78% at 80 ppm.

The systemic LOEL was established at 80 ppm (5.4 mg/kg/day in males and 6.6 mg/kg/day in females) based on decreased body weights. The NOEL was established at 10 ppm (0.62 mg/kg/day in males and 0.75 mg/kg/day in females).

The LOEL for ChE inhibition was established at 10 ppm (0.62 mg/kg/day in males and 0.75 mg/kg/day in females) based on significant inhibition of plasma (32 to 39% in males and 49 to 58% in females), erythrocyte (17 to 35% in males and 19 to 35% in females) and brain (50 to 53% in males and 49% in females) ChE activities. The NOEL was established at 1 ppm (0.062 mg/kg/day in males and 0.074 mg/kg/day in females).

I. Dermal Absorption

In a dermal absorption study [MRID No. 001638631; HED Doc. No 005689], radiolabeled ODM (^{14}C-ODM), at a single dose level of 2 mg/kg, was administered dermally or by i.v. injection to three Sprague-Dawley rats per sex per group per time period. Animals were sacrificed 2, 4, 8, 12, 24, 48 and 72 hours or until the radioactivity in urine dropped to two times background. For the dermally treated animals, a 12 cm^2 area of the application site was removed, washed and counted. For each time period, radioactivity was counted in urine, plasma, the skin, skin solvent wash samples.

The plasma half-life of ODM was 2 hours in both males and females following i.v. administration, and 3 hours in males and 4 hours in females following dermal exposure. For i.v. administration, the urine half-live was 5 to 14 hours in males and 2 to 20 hours females; and for the dermal exposure, 5 to 10 hours in males and 4 to 9 hours in females. Total recoveries for i.v. route of administration were 67% for males and 81% for females. For the dermal route of exposure total recoveries were 33% for males and 41% for females. Recoveries of ODM were low, probably due to metabolism and failing to include residual total body counts.

Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates, as calculated by regression analysis based on mg equivalents of ^{14}C-ODM over

time, were 0.15 µg/cm^2/hour for males and 0.17 µg/cm^2/hour for females.

j. Other Toxicological Considerations (Special Studies)

1) 7-Day Dermal Toxicity Study in the Rat: In this study (No MRID No., preliminary data submission by the registrant), ODM was administered dermally in water to Sprague-Dawley rats (10/sex/dose) at doses of 0, 1.5, 5.0, 10.0 or 20.0 mg/kg/day, 6 hours/day, for 7 days.

All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Further, no body weight decrements or effects on food consumption occurred. At terminal sacrifice, no treatment-related gross necropsy findings were reported.

At day 7, statistically significant inhibition of Erythrocyte and brain ChE activities were observed, plasma ChE activity was not inhibited by treatment. Erythrocyte ChE activity of males dosed at 10 and 20 mg/kg/day was inhibited by 12% and 25%, respectively, and brain ChE activity by 8.2 and 12%, respectively. Brain ChE activity in females was inhibited by 14% at 20 mg/kg/day. Plasma ChE activity in males and females and Erythrocyte ChE activity in females were comparable to control values.

Based on the results of this study (inhibition of Erythrocyte and brain ChE in males (12% and 8.2%, respectively) the LOEL was established at 10 mg/kg/day. the NOEL was established at 5 mg/kg/day.

2) Subacute (14-Day) Toxicity Studies in the Rat: In three separate studies, ChE activity was measured in Sprague-Dawley rats (5/sex/dose) following either oral gavage, feeding or dermal administration of ODM (94.6%) for 14 days. For each study plasma and erythrocyte ChE activities were determined at days 0, 7 and 14 and brain ChE, at study termination (day 14). Animals were observed daily for clinical signs of toxicity.

14-Day Oral (Gavage) Study: For the gavage study, rats were treated with ODM in water at doses of 0, 0.15, 0.45, and 2.5 mg/kg/day [MRID No. 40499303; HED Doc. No. 012222]. No clinical signs of ChE inhibition or other toxic signs were noted during the study or pathology at necropsy. Treatment-related inhibition of plasma, erythrocytes and brain ChE activities was observed during the study. At day 0, no inhibition was seen at any dose in plasma ChE activity in males and females or erythrocyte ChE activity in females. Erythrocyte ChE activity was inhibited by 11% and 15% in males dosed at 0.45 and 2.5 mg/kg/day, respectively. At day 7, plasma ChE was inhibited 17 and 37% in mid- and high-dose males, respectively, and 55% in high-dose females. At day 7, erythrocyte ChE activities were all significantly inhibited for low- (9% in males and 7% in females), mid- (20% in males and 16% in females), and high- (43% in males and 45% in females) dose animals. The day 14 evaluations showed significant inhibition of plasma ChE activities by 16%, 29%, and 45% in low-, mid- and high-dose males, respectively and by 31% and 60% in mid- and high-dose females, respectively. Erythrocyte ChE was significantly inhibited in mid- and high-dose males (28% and 49%, respectively) and low-, mid- and high-dose females (9%, 25%, and 48%, respectively). Brain ChE activity was inhibited in low- (11%, males and

females), mid- (29% in males and 23% in females) and high- (68% in males and 66% in females) dose animals.

The LOEL was established at 0.15 mg/kg/day, based on 11% inhibition of erythrocyte and brain ChE in males and females. The NOEL was not established.

14-Day Dietary Study: In another study, rats were fed diets containing ODM at 0, 3, 9, or 50 ppm (males: 0, 0.22, 0.60, or 3.2 mg/kg/day; females: 0, 0.20, 0.56 or 3.0 mg/kg/day) [MRID No. 40499302; HED Doc. No. 012222]. No clinical cholinergic signs were seen. On day 0, no inhibition of plasma or erythrocyte ChE was observed at any dose level in either males or females. After seven days of treatment, significant inhibition of plasma ChE activity was observed in mid- and high-dose males (34% and 70%, respectively) and low-, mid- and high-dose females (17%, 45%, and 83%, respectively). Erythrocyte ChE activity was also significantly inhibited in low-, mid- and high-dose males (9%, 32%, and 51%, respectively) and mid- and high-dose females (22% and 47%, respectively). On the day 14 evaluation, erythrocyte and brain ChE activities were significantly inhibited in all dose groups. Erythrocyte ChE activity was inhibited by 16%, 36%, and 50% in low-, mid-, and high-dose males, respectively, and by 12%, 29%, and 50%, in females, respectively. Brain ChE activity was inhibited by 20%, 57%, and 82% in low-, mid-, and high-dose males, respectively, and by 12%, 36%, and 79%, in females, respectively.

The LOEL was established at 3 ppm (0.22 mg/kg/day in males and 0.20 mg/kg/day in females), based on inhibition of erythrocyte and brain ChE activity. The NOEL was not established.

14-Day Dermal Study: In a 14-day dermal toxicity study [MRID No. 40499304; HED Doc. No. 012222], ODM was applied to the skin of Sprague- Dawley rats (5/sex/dose), 6 hour per day, for 14 days at 0, 0.3, 1.0, and 5.0 mg/kg/day. No effects were seen on bodyweight or food consumption. No treatment-related effects were seen during clinical observations or necropsy. At day 0, no biologically significant inhibition of plasma or erythrocyte ChE activities were seen in any of the treated males and females. On day 7, only animals in the high-dose group had significant inhibition of plasma (38% in males and 40% in females) and erythrocyte (26% in males and 40% in females) ChE activity. At day 14, high-dose males showed significant inhibition of 37% for erythrocyte ChE, while high-dose females showed significant inhibition of 55% for plasma and 46% for erythrocyte ChE activities. Brain ChE activity, measured at day 14, was significantly inhibited in mid- and high-dose males (12 and 48%, respectively) and low-, mid- and high-dose females (11, 16 and 60%, respectively).

The LOEL was established at 0.3 mg/kg/day in females and 1.0 mg/kg/day in males, based on inhibition of brain ChE in females (11%) and males (12%). The NOEL was not established in females, while the NOEL was established at 0.3 mg/kg/day in males.

3) 90-Day Brain ChE Study in the Rat: Because no NOEL for brain ChE was established in the chronic toxicity/oncogenicity study (see section c.1), additional data on brain ChE activities were requested. In this study [MRID Nos. 44141301, 40865203; HED Doc No. 012216], ODM

(50% concentrate in MIBK) was administered in the feed to 30 Sprague-Dawley rats per sex per group for 13 weeks at levels of 0, 0.10, 0.3, 1.0, 10 or 80 ppm of [males: 0, 0.0060, 0.018, 0.062, 0.620 or 5.4 mg/kg/day; females: 0, 0.0073, 0.022, 0.074, 0.75 or 6.6 mg/kg/day]. Brain ChE activity was determined at weeks 4, 8 and 13 on 10 rats per sex per time period per dose group.

Brain ChE was statistically significantly inhibited in males and females at 10 and 80 ppm at week 4, 8 and 13. At the 10 ppm, brain ChE activity was inhibited 53% in males and 49% in females at week 4, 50% in males and 49% in females at week 8, and 51% in males and 50% in females at week 13. At 80 ppm, brain ChE activity showed more severe dose related inhibition at weeks 4, 8 and 13 (78%, 77%, and 78%, respectively, in males and 78%, 77%, and 78%, respectively, in females). Brain ChE was not inhibited in males and females dosed at 1 ppm or lower.

The LOEL was established at 10 ppm (0.62 mg/kg/day in males and 0.75 mg/kg/day in females) based on inhibition of brain ChE activity (approximately 50% in males and females at weeks 4, 8 and 13). The NOEL was established at 1 ppm (0.062 mg/kg/day in males and 0.074 mg/kg/day in females).

4) Male Fertility Studies

Reversibility of Epididymal Vacuolation and Determination of Sperm Counts, Morphology and Motility: ODM was administered in the diet to groups of 9 to 10 male, Sprague-Dawley rats at 0, 3, 9 or 50 ppm for 0, 2, 3.5, 4, 6 and 8 months [MRID No. 40463001, 41834003; HED Doc. Nos. 006228, 006596, 012215]. Sperm counts, morphology and motility were determined at the end of 2, 4, 6 and 8 months. Necropsy was conducted on all animals, testes were weighed, and along with the epididymides, were examined histologically. Some groups of 9 to 10 rats were dosed at 50 ppm for 3.5, 4, 6 and 8 months and allowed to recover on control diet for 18 days, 2, 3, 4 or 5 months. The control rats used were generally rats dosed for the same length of time. After the recovery period, the animals were examined histologically. Plasma, erythrocyte and brain ChE activities were also determined.

No treatment-related effects were seen in mortality, clinical signs, food consumption, body weights or testes weights.

Sperm counts and motility were not biologically different from controls in any group. However, a large number of abnormal sperm (up to 58%) and non-motile sperm (up to 69% in controls) decreased the sensitivity of the study.

No treatment-related histological effects were seen in the testes. The epididymides showed vacuolation. At 9 ppm, minimal epididymal vacuolation was seen after 6 months in 1/9 animals and after 8 months in 5/9 animals. Severe epididymal vacuolation was seen in all animals dosed for 2, 4, 6 and 8 months at 50 ppm. The incidence and histologically grade of the lesion were considered dose-related. Animals dosed at 50 ppm for 6 months and allowed to recover unposed for 3, 4, and 5 months showed less severe vacuolation, but 2/4, 1/5, and 2/9 animals, respectively,

did not completely recover from the epididymal vacuolation in the 3 and 4 months recovery groups, respectively.

Inhibition of erythrocyte (12 to 53%) and brain (15 to 78%) ChE activities were statistically significantly depressed at all dose levels and time periods. Plasma ChE was not inhibited at either 3 and 9 ppm after 2 months dosing, at 3 ppm after 4 or 6 months dosing, or in any of the recovery groups dosed at 50 ppm. In groups recovering for 18 days after being dosed at 50 ppm for 3.5 months, brain ChE was significantly inhibited (10-47%). In these same recovering groups, erythrocyte ChE was significantly inhibited only in the group recovering for 18 days. In the group recovering for 2 months after being dosed at 50 ppm for 4 months erythrocyte ChE did not differ from control values.

The LOEL was established at 9 ppm (approximately 0.45 mg/kg/day) based on evidence of epididymal vacuolation seen after 6 and 8 months exposure. The NOEL was established at 3 ppm.

The LOEL for ChE inhibition was established at 3 ppm (approximately 0.15 mg/kg/day) based on inhibition of erythrocyte and brain ChE at all time periods. The NOEL was not established.

Evaluation of Sperm Motility in the Rat Following One, Two, or Three Months Dietary Exposure: ODM, technical (91.6 to 93.6%), was administered in the feed to 40 male Sprague-Dawley rats per group at 0, 3, 9, or 50 ppm (0, 0.13, 0.38, or 2.0 mg/kg/day) [MRID No. 41834002; HED Doc. No. 012221]. These rats were 9 weeks old at initiation of dosing. Ten males per group were sacrificed after 0, 1, 2, or 3 months of treatment. Sperm motility, epididymal and testes histology and selected organ weights were determined. Sperm motility, epididymal vacuolation and testes histopathology were determined at 0-, 1-, 2- and 3-months dosing.

Body weights were statistically significantly depressed by 12% at 1 month.

No statistically significant or biologically significant effects occurred on sperm motility. Neither the absolute nor relative testes weights were decreased. No dose-related histological findings in the testes were reported at any sacrifice time. At 50 ppm, epididymal vacuolation occurred in the 30/30 males in all treatment periods and at 9 ppm, in 1/10 at 2-months and 3/10 at 3-months. The effect at 9 ppm was minimal and did not occur at the 1-month sacrifice.

Plasma , erythrocyte, and brain ChE were statistically significantly reduced in all dose levels.

The LOEL was established at 9 ppm (0.38 mg/kg/day) based on increased incidence of epididymal vacuolation at 2 (1/10) and 3-months (3/10). The NOEL was established at 3 ppm (Lowest dose tested).

For ChE LOEL was established at 3 ppm (0.13 mg/kg/day) based on inhibition of

erythrocyte and brain ChE activity. The NOEL for ChE inhibition was not established.

Reproductive Toxicity Study with Treated Males and Untreated Females: In another non-guideline male fertility study [MRID No. 42499001, 42500101; HED Doc. No. 010117], ODM technical (92.5%) was administered to male Sprague-Dawley rats (main study: 30/dose, ChE substudy: 10/dose) at dietary levels of 0 or 50 ppm (1.9 mg/kg/day) for 10 weeks. These males were then mated with untreated females (30/group). Females were sacrificed on GD 20, corpora lutea and implantation sites were determined. Mating and fertility indexes, pre- and post-implantation losses and number of live fetuses per litter were determined. ChE activities were determined on 10 dosed males at week 10.

No treatment-related effects were observed on any of the parameters evaluated. Neither male fertility nor fertility indexes were affected.

Histopathological examination revealed epididymal vacuolation in the corpus epididymis of all of the treated males.

In a previous two-generation reproduction study (see section e.1)), fertility effects, litter and pup effects were noted at 50 ppm ODM. This study demonstrated that fertility effects noted in the two-generation study were due to effects on the female and not on the male. This study also demonstrates that epididymal vacuolation probably has no effect on fertility.

The male reproductive toxicity LOEL was established at 50 ppm (1.9 mg/kg/day), based on a decrease in testes weights and an increase in the incidence of corpus epididymal vacuolation; no effects on fertility were observed.

The ChE LOEL was 50 ppm (1.9 mg/kg/day), based on inhibition of plasma, brain, and erythrocyte ChE activity at 10 weeks.

5) 120-Day ChE Activity Study in Human Volunteers: Plasma and erythrocyte ChE activities were evaluated in 15 human volunteers administered ODM (97.5%) either acutely or repeated daily doses for up to 120 days [MRID No. 00039839; HED Doc. No. 012222]. Prior to the start of the study, all subjects were given physical, hematological and urological examinations. Plasma and erythrocyte ChE activities were determined prior to dosing to establish the mean activity and standard deviation for each subject; these values were used as the control values. ODM was administered orally using either undiluted in gelatin capsules or diluted with 25 mL of corn oil. In a pilot study, a single subject was treated at 0.4 mg/kg/day for five days; this subject formed the basis for the dose levels used in the study. For acute toxicity, seven subjects were treated with ODM, each received a dose of 0.0125, 0.025, 0.05, 0.25, 0.5, 1.0, or 1.5 mg/kg. For these subjects, ChE activities were measured at 0.5, 1, 2, 4, 8, or 24 hr, with additional measurements at 48 and 60 hr for subjects treated at 1.0 and 1.5 mg/kg. For the subchronic portion of the study, ChE activities were evaluated in four subjects treated for at 0.05 mg/kg/day for 25 to 30 days and two subjects treated for 60 days. A single subject was treated for 120 days at 0.1 mg/kg/day.

In the pilot study, a single subject was dosed at 0.4 mg/kg/day for five days. At 24 hr post dosing, plasma and erythrocyte ChE activities were inhibited by 50% and 35%, respectively.

Findings of the acute toxicity study showed that the NOEL was 0.5 mg/kg for both plasma and erythrocyte ChE. At 1.0 mg/kg plasma ChE was inhibited by about 18% and erythrocyte ChE by about 14%.

For the subacute study, volunteers treated at 0.05 mg/kg/day for 30 to 60 days, did not result in inhibition of either plasma or erythrocyte ChE. Treatment at 0.1 mg/kg/day for 120 days, resulted in a progressive inhibition of ChE activities. Plasma ChE was inhibited by 40% within the first two weeks of exposure; erythrocyte ChE was also progressively inhibited, reaching a plateau of 50% by day 60 of the 120 day exposure.

No cholinergic signs were noted in any of the subjects at anytime.

Based on the results of this study (inhibition of plasma ChE by 18% and erythrocyte ChE by 14%), the acute LOEL was established at 1.0 mg/kg. The NOEL was established at 0.5 mg/kg.

The LOEL for subacute toxicity was established at 0.1 mg/kg/day, based on one subject showing 40% inhibition of plasma ChE at two weeks and 50% inhibition of erythrocyte ChE at 60 days. The subacute NOEL was established at 0.05 mg/kg/day, based on no effects in six subjects at this dose.

6) *In vitro* ChE Inhibition Assays with ODM Metabolites: The inhibitory effects of ODM, 94.6% a.i., desmethyl ODM, 91.8%, desmethyl ODM sulfone, 96.2%, and chlorpyrifos-oxon as a positive control were tested in *in vitro* rat brain ChE assays [MRID No.: 44376701 and 44376702, HED Doc No.: none]. The IC_{50} for brain ChE activity was 2.71×10^{-6} M for ODM and 4.49×10^{-9} M for chlorpyrifos-oxon. Neither desmethyl ODM nor desmethyl ODM sulfone inhibited brain ChE over a concentration range of 1.00×10^{-9} M to 1.00×10^{-4} M. In conclusion, only ODM and chlorpyrifos-oxon inhibited ChE.

2. Dose/Response Assessment: Based on comprehensive evaluation of the toxicology data available on ODM, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below.

a. Special Sensitivity to Infants and Children

1) Recommendation for a Developmental Neurotoxicity Study: In the attempt to develop a weight-of-evidence recommendation on the need for developmental neurotoxicity testing with ODM, the following information was considered:

Evidence that support requiring a developmental neurotoxicity study:

ODM is a neurotoxic chemical.

Structure Activity Relationships: ODM is an organophosphate.

Administration to various species (rat, mouse, dog, monkey) results in progressive ChE inhibition in the plasma, erythrocyte, and brain. Adequate characterization of the ChE inhibition response has been conducted.

Delayed neuropathy (axonal degeneration) was observed in the acute delayed neurotoxicity study in hens.

Some data suggest that ODM may disrupt neuroendocrine function. For instance, in the two-generation reproduction study in rats, infertility of non-defined origin was observed at 50 ppm (2.1 mg/kg/day), along with decreased testes and ovarian weights, epididymal vacuolation, and decreased sperm motility. The data are not inconsistent with a CNS or hormonal effect, although a direct effect on the male and/or female productive organs cannot be ruled out. Alterations of ovarian and/or testicular weight was also observed in long-term toxicity studies in rats, mice, and dogs.

Evidence that do not support asking for a developmental neurotoxicity study:

No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either Sprague-Dawley rats, or American Dutch rabbits, at maternal gavage doses up to 4.5 or 0.8 mg/kg/day, respectively. Although an apparent treatment-related increase of the brain malformation hypoplasia of the telencephalon was noted in a developmental toxicity study in Long Evans rats, these results were found to be equivocal because of the high historical incidence of brain malformations in this strain at the time of study conduct. In the two-generation reproduction study in rats, no clinical evidence suggestive of neurotoxicity was observed grossly in pups, which had been administered ODM *in utero* and during early and late postnatal development, generally mediated by maternal dietary exposure, but also available in the diet to late lactation pups.

A postnatal segment of the developmental toxicity study in Sprague-Dawley rats assessed the functional development of animals that had been treated *in utero* with ODM. This study was essentially equivalent to a developmental neurotoxicity study, except that pups were not treated postnatally via maternal milk, and neither assessment of memory nor neurohistological examination were performed. No effects of treatment were observed.

Assessment of differential response of offspring versus adults to ChE inhibition following treatment with ODM:

In the two-generation reproduction study in rats, inhibition of plasma, erythrocyte, and brain ChE was observed in post-natal days 4 and 21 pups at doses equivalent to those at

which inhibition was observed in the adults.

In the developmental toxicity study in rats, brain ChE was not inhibited in GD 20 fetuses, although significant inhibition of ChE activities (plasma, erythrocyte, and/or brain) were observed in the dams at GD 16 and GD 20.

Based upon the weight-of-evidence described, the HIARC report (May 7, 1998, HED Doc. No.: 012606) did not recommend that a developmental neurotoxicity study in rats be required for ODM at this time. This issue should, however, be referred to the OP Data Needs Committee for further consideration.

2) Adequacy of Data Package: The data package included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. Numerous additional studies have been submitted by the Registrant to further assess treatment-related toxicity on male reproduction. A review of the mutagenicity data raised concerns regarding the potential of ODM to result in heritable effects; the lack of these data was considered a data gap by the SARC.

3) Susceptibility Issues: The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to ODM. In a 1985 two-generation reproduction study in rats, the NOEL for both the parental animals and the offspring was 1 ppm (0.05 mg/kg/day). Toxicity to the offspring at the LOEL of 10 ppm (2.5 mg/kg/day) consisted of pup mortality and decreased postnatal body weights, which occurred in the presence of parental toxicity (decreased body weight gain in males and females). In the 1990 two-generation reproduction study in rats, the parental and offspring systemic NOELs were equivalent at 9 ppm. Decreased litter size and pup weight were observed at the LOEL of 50 ppm (2.1 mg/kg/day) in the presence of parental systemic and reproductive toxicity (decreased body weights, decreased male and female fertility, testes and ovarian weight reduction, decreased number of dams with corpora lutea, increased estrous cycle length). Measures of ChE activity demonstrated that inhibition occurred in the offspring (post natal days 4 and 21) at the same dose as it was observed in the adults (also described in Eigenberg et al., 1996, *Toxicologist* 30:310). In both the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was not observed, although the doses administered produced evidence of systemic toxicity in the maternal animals. In the rats, decreased body weight and food consumption, transient tremors, and plasma, brain, and erythrocyte ChE inhibition were observed in the dams, while measures of brain ChE in GD 20 fetal rats did not demonstrate inhibition (also described in Astroff et al., 1996, *Toxicologist* 30:191); in the rabbits, erythrocyte and brain ChE inhibition were observed in the does.

The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to ODM. Therefore, an additional Uncertainty Factor is not warranted.

b. Reference Dose (RfD)

Study Selected: Non-guideline ChE inhibition study in human volunteers

MRID No.: 00039839

Executive Summary: 120-Day ChE Activity Study in Human Volunteers: Plasma and erythrocyte ChE activities were evaluated in six human volunteers given OMD (97.5%) for up to 120 days [MRID No. 00039839; HED Doc. No. 012222]. Pre-dosing plasma and erythrocyte ChE activities were determined to establish the baseline mean activity and standard deviation for each subject; these values were used as the control values. ODM was administered orally, either undiluted in gelatin capsules or diluted with 25 mL of corn oil. ChE activities were evaluated in four subjects treated at 0.05 mg/kg/day for 25 to 30 days and two subjects, for 60 days. A single subject was treated for 120 days at 0.1 mg/kg/day.

Treatment at 0.05 mg/kg/day for 30 to 60 days did not result in inhibition of either plasma or erythrocyte ChE. Treatment at 0.1 mg/kg/day for 120 days, resulted in a progressive inhibition of ChE activities. Plasma ChE was inhibited by 40% within the first two weeks of exposure; Erythrocyte ChE was also progressively inhibited, reaching a plateau of 50% by day 60 of the 120 day exposure.

No cholinergic signs were noted in any of the subjects at anytime.

Based on the results of this study (inhibition of plasma ChE by 18% and Erythrocyte ChE by 14% in a single human volunteer), the LOEL was established at 0.1 mg/kg/day. The NOEL was established at 0.05 mg/kg/day.

Dose/Endpoint for establishing the RfD: NOEL = 0.05 mg/kg/day based on one subject showing 40 % inhibition of plasma ChE at 2 weeks and 50% Erythrocyte ChE inhibition at 60 days. LOEL = at 0.1 mg/kg/day.

Comments about Study and Endpoint: The HIARC re-affirmed the dose and endpoints selected for establishing the RfD in 1998 (May 7, 1998, HED Doc. No.: 012606).

Uncertainty Factor (UF): 100 (10X for intra-species variability, 10X FIFRA safety factor for data gap in lieu of a specific locus test).

$$\textit{Chronic RfD} = \frac{\textbf{0.05 } \textit{mg/kg/day } \textbf{(}\textit{NOEL}\textbf{)}}{\textbf{100 (}\textit{UF}\textbf{)}} = \textbf{0.0005 } \textit{mg/kg/day}$$

c. Carcinogenic Classification and Risk Quantification

1) Combined Chronic Feeding/Oncogenicity in the Rat: In a combined chronic feeding/oncogenicity study, ODM (52% a.i. in MIBK) was administered in the feed at nominal

concentrations of 0, 2, 20, or 200 ppm (analytically confirmed doses of 0, 0.57, 4.6, or 52 ppm of a.i., equivalent to 0, 0.027, 0.224 or 3.04 mg/kg/day, respectively, in males and 0, 0.036, 0.284 or 3.60 mg/kg/day, respectively, in females) to Fischer 344 rats (50 rats/sex/dose, an additional 5 rats/sex/dose were assigned to a ChE substudy) for 118 weeks. Plasma and erythrocyte ChE activities were determined after 4 and 118 weeks of treatment. After 4 weeks of treatment, the ChE substudy animals were sacrificed for determination of plasma, erythrocyte and brain ChE activities. At study termination (week 118), plasma, erythrocyte, and brain ChE activities were measured on randomly selected animals (5/sex/dose)(MRID Nos. 00151806, 40865203, 40865201, 40865202 and 44141301).

Treatment-related systemic effects were limited to high-dose males and females and consisted of changes in mean body weights, food consumption and absolute and relative organ weights. Body weights of high-dose animals were statistically significantly depressed at weeks 26 (males only), 52, 78, and 104. Mean body weights of high-dose animals progressively decreased during the study. At week 104 decreases of 17% were observed in males and 14%, in females. Despite the decreases in mean body weight, food consumption for high-dose males and females was statistically significantly increased at weeks 26, 52, 78 (females only) and 104. Changes in tissue weights consisted of increases in absolute brain and ovarian weights and relative brain weight. At the high-dose, absolute testes weights were increased to 120% of control values, while absolute ovarian weights may have been decreased to 32% of control value (neither was statistically significant and judged to be equivocal responses). Nominal, but not statistically significant, increases in retinal degeneration occurred in females, but not in males, at the high-dose. Statistically significant inhibition of plasma, erythrocyte and brain ChE activities were observed after four and 118 weeks of treatment. After four weeks of treatment, plasma ChE activity was inhibited in mid-dose females (42%) and high-dose males (64%) and females (86%). At this same time point, erythrocyte ChE was inhibited in mid- and high-dose males (29% and 44%, respectively) and females (34% and 47%, respectively); and brain ChE activity was inhibited in low- mid- and high-dose males (11%, 51% and 89%, respectively) and females (6.2%, 49%, and 88%, respectively). After 118 weeks of treatment, plasma and erythrocyte ChE activities were inhibited in mid- and high-dose animals, while brain ChE activity was inhibited at all dose levels. Plasma ChE activity was inhibited by 58% and 91% in mid- and high-dose, males, respectively, and 51% and 91%, in females, respectively. Erythrocyte ChE activity was inhibited by 54% and 83% in mid- and high-dose males, respectively, and 61% and 84% in mid- and high-dose females, respectively. Brain ChE activities were significantly inhibited at the low-dose (8.3% in males and 8.0% in females), mid-dose (53% in males and 50% in females), and high-dose (86% in males and 84% in females).

No treatment related neoplasia was observed in this study. ODM did not alter the spontaneous tumor profile in this study.

Because no NOEL was established for brain ChE activity, this study was initially graded as supplementary, pending results of a 90-day brain ChE study. The 90-day brain ChE study MRID Nos. 44141301, 40865203; HED Doc No. 012216],was found to be acceptable.

Based on the results of this study (decreases in body weights of 17% in males and 14% in females), the systemic LOEL was established at 52 ppm (3.04 mg/kg/day in males and 3.60 mg/kg/day in females). The systemic NOEL was established at 4.6 ppm (0.224 mg/kg/day in males and 0.284 mg/kg/day in females).

Based on the results of this study (inhibition of brain ChE by 8.3% in males and 8.0% in females), the ChE LOEL was established at 0.57 ppm (0.027 mg/kg/day in males and 0.036 mg/kg/day in females). The ChE NOEL was not established.

2) Oral (Feeding) Oncogenicity Study in Mice: In this study, ODM (91.6 to 94.2%) was administered in the diet of CD-1 mice (50/sex/dose) at 0, 3, 15 or 50 ppm (0, 0.5, 2.3 or 7.8 mg/kg/day in males and 0, 0.6, 2.9 or 8.9 mg/kg/day in females) for 21 months. Organs and tissues were examined histologically for pathological changes, including tumors. Plasma, erythrocyte and brain ChE activities were determined after 12, 18 and 21 months of treatment [MRID No.: 42576601].

Systemic toxicity was limited to animals treated at the mid- and high-dose levels. At the high-dose, the mean body weight of males was slightly, but significantly, decreased; the decreases, however, were not of biological importance (4% to 7%). An increased incidence of clonic convulsions in both sexes was observed at the high-dose. At the mid-dose level, increased incidence of inflammation, ulceration and acanthosis of the pinnae of the ears was observed in both sexes. Also seen at this dose level were histological changes in males, which consisted of vacuolation of the epithelial cells of the epididymis. No systemic toxicity was observed at the low-dose level.

Statistically significant inhibition of plasma, erythrocyte and brain ChE activities were observed during the study. At the low-dose level, plasma ChE activity was significantly inhibited in females by 21 to 22% after 12 and 18 months of treatment; males were unaffected at this dose level. Erythrocyte ChE activity in low-dose animals was significantly inhibited in males (9% to 17%) and in females (10% to 12%). Plasma ChE activity was inhibited at the mid-dose males (50 to 54%) and females (50 to 62%) and high-dose males (80 to 86%) and females (82 to 89%). Erythrocyte ChE activity was also significantly inhibited at the mid-dose (34 to 40% in males and 25 to 38% in females) and high-dose (39 to 45% in males and 39 to 48% in females) levels. Analysis of brain ChE activity at month 21 revealed statistically significant inhibition at the low-dose (11% in males and 17% in females), mid-dose (51% in males and 48% in females) and high-dose (73% in males and 63% in females) levels.

No compound-induced carcinogenic response was observed under the conditions of the study. Adequate dose levels were used to assess the carcinogenic potential of ODM.

Based on the results of this study (increased incidence of cytoplasmic vacuolation in the epididymides in males and increased inflammation, ulceration and acanthosis of the pinnae of the ears in both sexes), the LOEL for systemic toxicity was established at 15 ppm (2.3 mg/kg/day in males, and 2.9 mg/kg/day in females). The NOEL for systemic toxicity was

established at 3 ppm (0.5 mg/kg/day in males and 0.6 mg/kg/day in females).

Based on the results of this study (inhibition of brain and erythrocyte ChE activity in both sexes and plasma ChE activity in females), the ChE LOEL was established at 3 ppm (0.5 mg/kg/day in males and 0.6 mg/kg/day in females). The ChE NOEL was not established.

d. Developmental Classification:

1) Developmental Toxicity Study in the Rat: In a developmental toxicity study in the, ODM (90.6%) was administered by gavage to Sprague-Dawley rats at dose levels of 0, 0.5, 1.5, or 4.5 mg/kg/day on GD 6-15 (MRID 00146812, 00158342, HED Doc. No. 012220, 004822, 005585).

Maternal toxicity was demonstrated at the high-dose level and consisted of slight, but statistically significant, decreases in mean body weight of 2.6% on GD 12 and 3% on GD 12. A statistically significant decrease in mean body weight gain (11.5%) was observed from GD 6 to 20. Food consumption was decreased by 8% on GD 8 and 6% on GD 12. Clinical signs (transient tremors) were also observed in essentially all (98%) of the high-dose dams.

Maternal plasma, erythrocyte and brain ChE activities were evaluated on GD 16 and 20. On GD 16, ChE activity was inhibited at the low-, mid- and high-dose levels by 30%, 54%, and 72%, respectively, for plasma and 21%, 52%, and 68%, respectively, for brain. Erythrocyte ChE was inhibited by 37% at the mid-dose level and by 56% at the high-dose level. On GD 20, marked inhibition of brain ChE was still apparent at the low- (19%), mid- (38%) and high- (54%) dose levels. Erythrocyte ChE was inhibited at the high-dose level by 40%, while plasma ChE activities were unaffected.

No developmental toxicity or inhibition of fetal brain ChE was observed at the highest dose tested. Further, no effects were observed in any of the developmental indices, reflex evaluation, maze learning or open field activity at any dose level.

Based on the results of this study (inhibition of plasma ChE by 30% and brain ChE by 21% on GD 16), the maternal LOEL was established at 0.5 mg/kg/day. The maternal ChE NOEL was not established (less than 0.5 mg/kg/day, low dose tested).

The LOEL for developmental toxicity was not established (greater than 4.5 mg/kg/day); the NOEL for developmental toxicity was established at 4.5 mg/kg/day, the highest dose tested. No effects were noted in fetal brain ChE activities at GD 20.

2) Developmental Toxicity Study in the Rabbit: In another developmental toxicity study, ODM was administered by gavage at dose levels of 0.05, 0.2, or 0.8 mg/kg/day (adjusted for concentration) to American Dutch rabbits on GD 7-19 (MRID 00146989, 00153606, 42859901; HED Doc. No. 003844, 011394, 012220). In another developmental toxicity study [MRID Nos.

00146989, 00153606, 42859901; HED Doc. Nos. 003844, 004437, 011394, 012220], ODM (53.5% a.i. in MIBK) was administered by gavage at 0, 0.1, 0.4, or 1.6 mg/kg/day (0, 0.05, 0.2 or 0.8 mg a.i./kg/day) to 17 presumed pregnant American Dutch rabbits from GDs 7 to 19. Rabbits were weighed on GDs 0, 7, 10, 14, 17, 21 and 28. At GD 28, rabbits were sacrificed, and corpora lutea, implantation sites, and live and dead implants were counted. In a separate ChE substudy, plasma, erythrocyte and brain ChE activities were determined on five randomly selected does per group at GDs 20 and 28; the rabbits were dosed by gavage at 0, 0.05, 0.2 or 0.8 a.i. mg/kg/day. All fetuses were examined for external, visceral and skeletal abnormalities.

Doses for the main study were selected, based on the results of a range-finding study in which rabbits (2 to 3/dose) were administered ODM at 0.05, 0.25, 0.5, 1.5, 3.0, or 6.0 mg a.i./kg/day from GD 6 to 19. Observed clinical signs included mortality in all three animals dosed at 6 mg/kg/day and one out of three animals dosed at 3 mg/kg/day. The two surviving animals at 3 mg/kg/day lost considerable of body weight. No post-implantation losses were observed at 0.5 mg/kg/day and lower doses, while post implantation losses at doses of 1.5, 3.0, or 6.0 mg/kg/day were 42, 83 and 100%, respectively. Based on the results of this range-finding study, doses of 0.05, 0.2 or 0.8 mg a.i./kg/day were selected for the main study.

In the definitive study, clinical signs of toxicity included loose stools in 5/17 dams dosed at 0.2 mg/kg/day and 8/17 dams dosed at 0.8 mg/kg/day, these effects were judged to be of equivocal biological significance. No treatment-related changes were seen in either the maternal body weight or body weight gain during the gestation period.

Litter size, fetal viability and weight were not affected at any dose level. Soft tissue abnormalities occurred in control and high-dose animals with similar frequencies and with no dose-response relationship. No developmental toxicity was observed at the skeletal examination of the fetuses. Slight increases in incomplete ossification of the metacarpals were observed at all dose levels (14.1 to 17.6% of treated fetuses affected compared to 4.2% for control fetuses). This finding, however, was considered to be equivocal and incidental to the study, since this finding is a variable parameter and lacked a clear dose-response relationship in this study.

Maternal ChE activities were determined on GDs 20 and 28 (9 days post-dosing). No inhibition of plasma ChE was noted at any time period or dose level. At the high-dose level, erythrocyte and brain ChE were statistically significantly inhibited by 43% and 21%, respectively, on GD 20. On GD 28, plasma, erythrocyte and brain ChE activities of the treated dams were comparable to control values.

Based on the results of this study (inhibition of erythrocyte ChE by 43% and brain ChE by 21% on gestation day 20), the maternal LOEL was established at 0.8 mg/kg/day. The maternal NOEL was established at 0.2 mg/kg/day.

The developmental toxicity LOEL was not established (greater than 0.8 mg/kg/day), the NOEL was established at 0.8 mg/kg/day.

The reproductive/developmental toxicity issues of ODM were addressed by the HED Reproductive and Developmental Toxicity Peer Review Committee on September 29, 1992. The Committee concluded that "clear evidence of reproductive toxicity was found in the rat in the form of decreased litter size and viability, decreased fertility, and decreased weight of the testes and ovaries. Epididymal vacuolation, although of uncertain biological significance, is assumed to be of concern and may be associated with the decreased fertility noted above. It was observed after 3 months of exposure at dose levels as low as 0.45 mg/kg/day. The NOELs resulting from long-term exposure in the rat reproduction studies range from 0.38 to 0.5 mg/kg/gay. The [Committee] did not consider the slight changes in reproductive parameters at those dose levels to be biologically significant. The NOEL in a short-term reproductive toxicity study (the "Dominant Lethal Plus" study) was 0.9 mg/kg/day. The latter study is the most appropriate study to use for the risk assessment of workers."

e. Dermal Absorption:

MRID No.: 001638631

Dermal Absorption Factor: Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates as calculated by regression analysis based on mg equivalents of ^{14}C-ODM over time were 0.15 μg/cm^2/hour for males and 0.17 μg/cm^2/hour for females.

Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates as calculated by regression analysis based on mg equivalents of ^{14}C-ODM over time were 0.15 μg/cm^2/hour for males and 0.17 μg/cm^2/hour for females [MRID No. 001638631; HED Doc. No 005689].

f. Other Toxicological Endpoints

1) Acute Dietary

Study Selected: 7-Day Dermal Toxicity Study in the Rat

MRID No. None assigned (preliminary data submission by the registrant)

Executive Summary: ODM was administered dermally in water to Sprague- Dawley rats (10/sex/dose) at doses of 0, 1.5, 5.0, 10.0 or 20.0 mg/kg/day, 6 hours/day, for 7 days.

All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Further, no body weight decrements or effects on food consumption occurred. At terminal sacrifice, no treatment-related gross necropsy findings were reported.

At day 7, statistically significant inhibition of Erythrocyte and brain ChE activities were observed, plasma ChE activity was not inhibited by treatment. Erythrocyte ChE activity of males

dosed at 10 and 20 mg/kg/day was inhibited by 12% and 25%, respectively, and brain ChE activity by 8.2 and 12%, respectively. Brain ChE activity in females was inhibited by 14% at 20 mg/kg/day. Plasma ChE activity in males and females and Erythrocyte ChE activity in females were comparable to control values.

Dose and Endpoint for Risk Assessment: NOEL = 5 mg/kg/day based on significant inhibition of Erythrocyte and brain ChE in males (12% and 8.2%, respectively) at 10 mg/kg/day (LOEL).

Comments about Study and Endpoint: For the 14-day dermal toxicity study, plasma and erythrocyte ChE activities were measured at 7 days and 14 days; while brain ChE activity was measured only at 14 days. In the 7-day dermal toxicity study, plasma, erythrocyte and brain ChE activities were all measured at 7 days. For this reason, the 7-day dermal toxicity study was selected over the 14-day dermal toxicity study. Further, there was no consistency in the results of the two studies (plasma and erythrocyte ChE inhibition at 5 mg/kg/day differed greatly between the two studies). The rationale provided by the Registrant were not adequate enough to reject the 14-day study as flawed.

Uncertainty Factor (UF): 100 (10X for intra-species variability and 10X for inter-species extrapolation).

This Risk assessment is required.

2) Short and Intermediate Term Occupational and Residential (1-7 days)

Study Selected: 14-Day Dermal Toxicity Study in the Rat

MRID No. 40499304

Executive Summary: ODM (94.6%), was administered dermally in water to five Sprague Dawley rats per sex per group, 6 hour per day, for 14 days at 0, 0.3, 1.0, and 5.0 mg/kg/day . Plasma ChE and Erythrocyte ChE activity was determined at day 0, 7, and 14. Brain ChE activity was determined at termination.

No effects were seen on body weight or food consumption. No treatment-related clinical findings or necropsy observations were observed. No biologically significant inhibition of plasma or erythrocyte ChE was observed in low-, mid- or high-dose males and females on day 0. At day 7, significant inhibition of plasma and erythrocyte ChE was observed in high-dose males (38% and 26%, respectively) and females (40% and 28%, respectively). At day 14, plasma ChE was inhibited only in high-dose females (55%), while erythrocyte ChE was inhibited in mid-dose females (11%) and high-dose males (37%) and females (46%). Brain ChE activity, measured at day 14, was inhibited in mid- and high-dose males (12% and 48%, respectively) and low-, mid- and high-dose females (11%, 16% and 60%, respectively).

Dose and Endpoint for Risk Assessment: NOEL = 0.3 mg/kg./day for brain ChE inhibition in males.

Comments about Study and Endpoint: This study was conducted via the appropriate route of concern (i.e., dermal) for this risk assessment.

Uncertainty Factor (UF): 100 (10X for intra-species variability and 10X for inter-species extrapolation).

3) Chronic Occupational and Residential (Non-Cancer)

Study Selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: Based on the current use pattern, there is minimal concern for long term dermal exposure potential/risk.

This risk assessment is NOT required

4) Inhalation Exposure:

Study Selected: Acute inhalation study in the rat (81-3)

MRID Nos. 40779805C and 40779805

Executive Summary: In an acute inhalation toxicity study, groups of young adult Sprague Dawley rats were exposed by the inhalation route to ODM (50% concentrate, 55.3% a.i. in 50% polyethylene glycol 400 and 50% ethanol) for 4 hours (nose only) at concentrations of 0.177, 0.224, 0.266, 0.370 or 0.540 mg/L. Animals then were observed for 14 days. The LC_{50} for males was 0.443 mg/L and for females was 0.427 mg/L. The NOEL was <0.177 mg/L or < 0.0979 mg a.i./L based on clinical signs (tremors) in males and females (note: dose levels should be multiplied by 0.553 to adjust for percent active ingredient).

Dose dependent mortality was seen at ≥ 0.266 mg/L in males and females. Death occurred on the day of dosing to day 5 after dosing. Most deaths occurred on day 0 to 2, with only 1 male dying on day 5 and 1 female dying on day 3. Tremors were seen in most males and females at all dose levels. In addition, hypoactivity and salivation were seen in most males and females at ≥ 0.224 mg/L. Clinical signs ended by day 7. There appeared to be body weight gain decreases in females at ≥ 0.370 mg/L and in males at ≥ 0.224 mg/L. Single necropsy findings occurred more frequently at ≥ 0.266 in males and ≥ 0.0.370 mg/L in females, such as salivation, turbinates red, ventrum staining and black zone in the glandular stomach mucosa. No compound related lesions were seen in animals that survived to day 14.

Dose and Endpoint for Risk Assessment: Dose=0.098 mg/L; the LOEL of 0.177 mg/L adjusted for percent active ingredient (0.177 x 0.553). A NOEL was not established.

Comments about Study and Endpoints: Since no other inhalation studies were available, the HIARC recommended that this dose be used for short, intermediate and chronic exposure risk assessments.

Uncertainty Factor (UF): UF = 300 (10X for interspecies extrapolation, 10X for intraspecies variability and 3X for the use of a LOEL (i.e., lack of a NOEL in the study).

This Risk assessment is required.

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	LOEL=2.5	Decreased Erythrocyte and brain ChE activity in males at day 0.	Acute Neurotoxicity in the rat
	UF=3000	**Acute RfD = 0.0008 mg/kg/day**	
Chronic Dietary	NOEL=0.05	Decreased plasma ChE	ChE study with human volunteers
	UF=100	**Chronic RfD = 0.0005 mg/kg/day**	
Carcinogenicity (Dietary)	OMD is classified as a **"Not Likely"** human carcinogen.		
Short-Term (Dermal)	NOEL=5.0	Decrease plasma, Erythrocyte and brain ChE	7-Day dermal toxicity study in the rat
	MOE = 100		
Intermediate-Term (Dermal)	NOEL=0.3	Decreased brain ChE	14-Day dermal toxicity study in the rat
	MOE = 100		
Inhalation (any time period)	LOEL = 0.177 mg/L	Clinical signs (tremors)	Acute Inhalation Study in the Rat
	MOE = 300		

For each of the exposure scenarios, an appropriate toxicology endpoints and toxicology study have been selected. The selected toxicology endpoints were consistent with organophosphate-induced toxicity (inhibition of ChE and resulting clinical signs of intoxication) and the studies

selected were appropriate for each exposure scenario. The acute and chronic dietary RfDs were based on an acute neurotoxicity study, in which rats were orally gavaged once with ODM, and a special ChE study in which human volunteers were given repeated oral doses of OMD. Special ChE dermal toxicity studies of seven and 14-days duration, specifically address the short- and intermediate-term dermal exposure scenarios.

IgnOff Date:	9/22/98
DP Barcode:	D235190
HED DOC Number:	012877
Toxicology Branch:	RRB2

S